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Catalytic Macrocyclization Strategies Using Continuous Flow: Formal Total Synthesis of Ivorenolide A.

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ABSTRACT A formal total synthesis of ivorenolide A has been accomplished employing a Z-selective olefin cross metathesis and a macrocyclic Glaser-Hay coupling as key steps. The macrocyclization protocol employed a phase separation/continuous flow manifold whose advantages include catalysis, fast reaction times, high concentrations and facile scale-up.

INTRODUCTION

Macrolides are a family of macrocyclic natural products having a wide array of biological activities.¹ From a synthetic perspective, several methods have evolved as the most popular candidates for macrocyclization. Macrolactonization² via stoichiometric activation of seco-acids, such as the Yamaguchi protocol,³ is without a doubt the most popular method for constructing the ester motif of macrolides. Another common synthetic route to form macrocycles involves carbon-carbon bond formation via transition metal catalysis, usually using olefin metathesis or

cross-coupling strategies.⁴ Despite the utility displayed by the above transformations, the macrocyclizations are usually performed at low concentration, and rely upon slow addition techniques. Consequently, scale-up of the target macrocycles becomes problematic,⁵ which is disappointing when promising biological activity is observed. The ivorenolides A⁶ and B⁷ are a unique class of macrolides which possess 1,3-diyne motifs isolated from the stem bark of *K. ivorensis* (Figure 1). Their immunosuppressive activities make them attractive targets for medicinal chemistry investigations given the need for new immunosuppressants with improved therapeutic profiles. Total syntheses of both the natural and unnatural enantiomers of ivorenolide A have appeared in the literature, each exploiting a macrolactonization employing stoichiometric activation strategies and high dilution and/or slow addition as the key macrocyclization step (Figure 1).^{6,8} As such, the development of alternative methods for macrocyclization that would employ catalysis, high concentrations and facilitate scale-up would be highly desirable.⁹ Our group has put forth an alternative strategy for the synthesis of macrocycles via Glaser-Hay coupling using a “phase separation” strategy.¹⁰ The protocol was shown to exploit aggregation effects caused by mixtures of poly(ethylene)glycol (PEG) co-solvents.¹¹ During the development of the “phase separation” technology, it was apparent that the substrate scope explored to date was limited, and did not address the influence of chiral centers, steric hindrance about the alkyne reaction centers or tolerance to common protecting groups. In addition, no investigation of the feasibility of scale-up of complex macrocycles at the gram scale had been demonstrated. To respond to the aforementioned questions, the formal total synthesis of ivorenolide A by application of the “phase separation” strategy under continuous flow techniques is described herein (Figure 1).

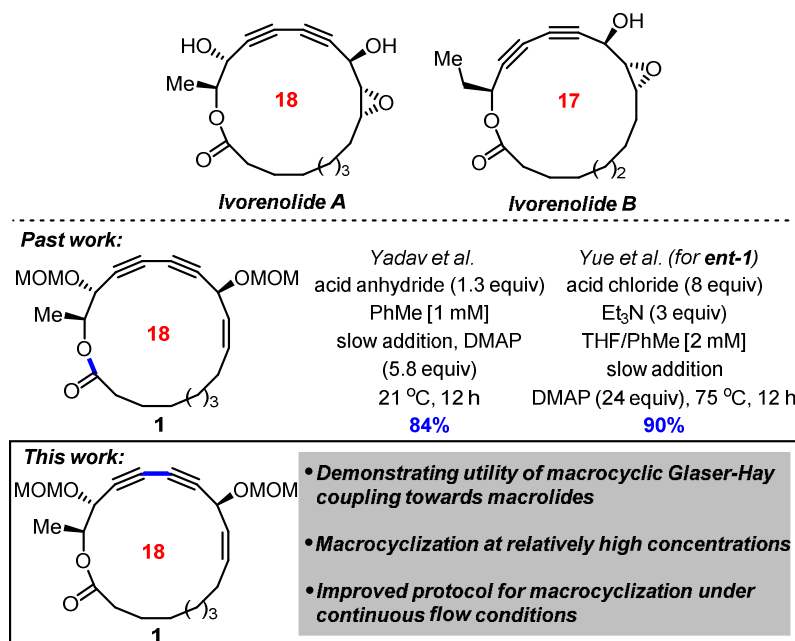


Figure 1. Macrocyclization strategies via continuous flow towards ivorenolide A. Ring sizes are in red.

RESULTS/DISCUSSION

The retrosynthetic analysis for the development of a phase separation/continuous flow macrocyclization towards the synthesis of ivorenolide A aimed to prepare the 18-membered macrolactone **1** intermediate, which was previously prepared by Yadav¹² and Yue⁶ as well as a simplified model **1a** (Figure 2). Envisioning the macrocyclization event arising from Glaser-Hay coupling of two terminal alkynes, the linear precursor **2** was selected as a target for the formation of macrocycle **1**, while the macrocyclization of the model 18-membered macrolactone **1a** was also imagined arising from Glaser-Hay coupling of linear precursor **2a**. Each ester (**2** and **2a**) could be prepared from esterification of the alcohol **3** with a corresponding carboxylic acid derivative.

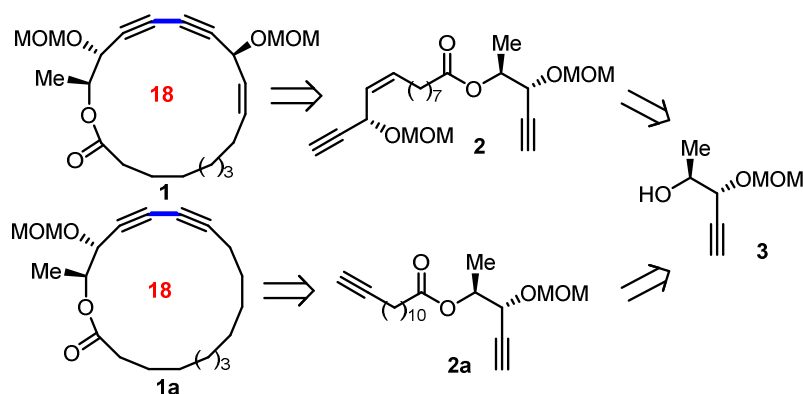
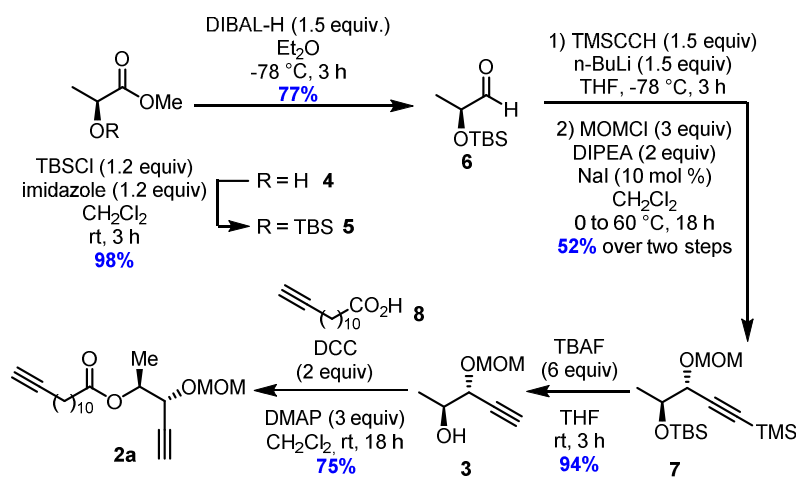


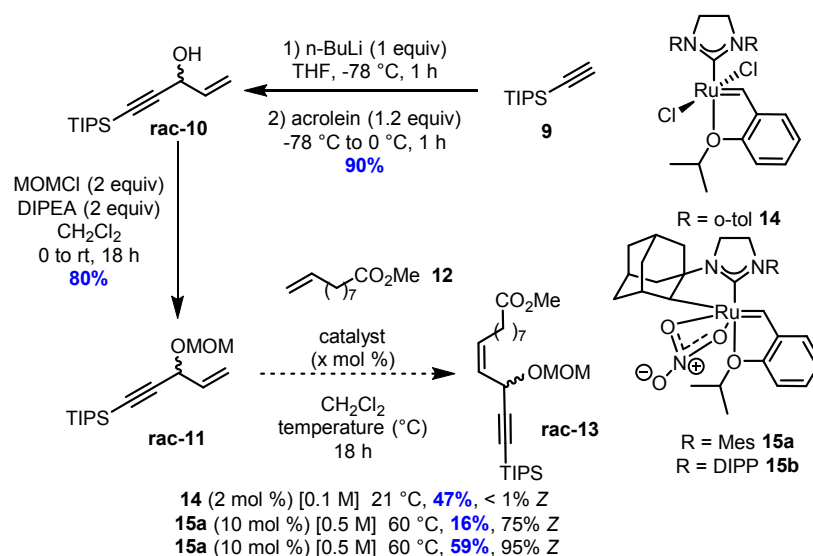
Figure 2. Retrosynthetic analysis towards the macrocyclic core of ivorenolide A (**2**→**1**) and a simplified model (**2a**→**1a**). Ring sizes are in red.

The synthesis of alkynyl alcohol **3** commenced from TBS-protected (*S*)-methyl lactate (Scheme 1). Reduction of the ester **5** to the corresponding aldehyde **6** using DIBAL-H and addition of the organolithium derived from trimethylsilyl acetylene afforded solely the desired diastereomer. Subsequent MOM-protection afforded the fully protected alkyne **7** in 52% yield over two steps. Removal of both silyl protecting groups provided **3** in 94% yield. Esterification of alcohol **3** using DCC/DMAP conditions with known carboxylic acid **8** provided the macrocyclization precursor **2a** in 75% yield.



Scheme 1. Synthesis of alcohol **3** and diyne **2a** analysis towards the macrocyclic core of ivorenolide A (**2**→**1**) and a simplified model (**2a**→**1a**).

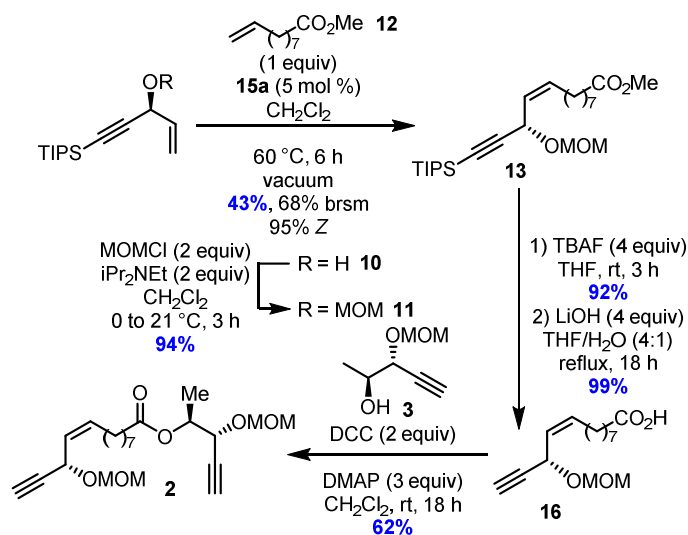
The carboxylic alkynyl synthon **1a** required for the synthesis of macrocycle **1** was then envisioned arising from a *Z*-selective cross metathesis process.¹³ The MOM-protected substrate **rac-11** could be prepared in two steps via alkylation of acrolein and subsequent protection from MOMCl. To test the synthetic route, several cross metathesis reactions were evaluated on the racemic, MOM-protected secondary alcohol **rac-11** (Scheme 2)



Scheme 2. Optimization of a *Z*-selective cross metathesis to prepare racemic **13**.

Cross metathesis was first evaluated with 1.0 equivalent of methyl ester **12** at room temperature using the Stewart-Grubbs catalyst **14**.¹⁴ The desired product **rac-13** was obtained in 47% yield and isolated as the pure *E*-isomer. Next, two Ru-based *Z*-selective catalysts were evaluated, each having a different NHC in which the *N*-aryl substituent differed.¹⁵ After a brief survey of reaction conditions,¹⁶ it was found that the DIPP-bearing catalyst **15b** at 10 mol%, 60 °C and at [0.5 M] afforded a 59% yield of the desired olefin **rac-13**, in excellent *Z*-selectivity (95% *Z*). Cross metathesis using the mesityl catalyst **15a**¹⁷ was not as selective (75% *Z*). With

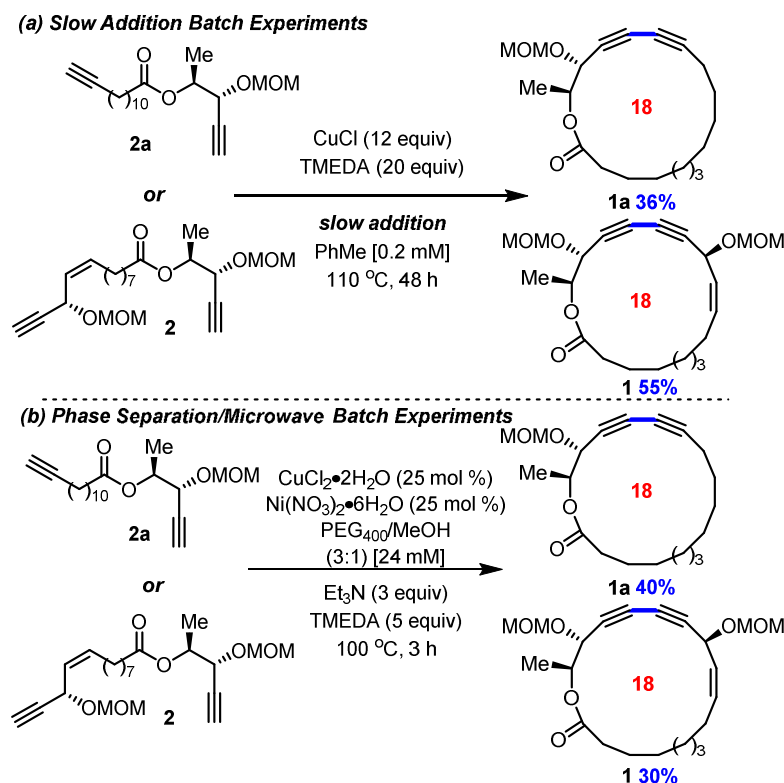
optimized conditions for the cross metathesis procedure in hand, the synthesis of the enantioenriched carboxylic acid **16** was undertaken (Scheme 3). First the enantiomerically pure alcohol **10** could be obtained via a previously reported CBS reduction, or via diastereomeric resolution.¹⁸ The alcohol **10** was protected as its MOM ether **11** in 94% yield and subsequently subjected to *Z*-selective cross metathesis. To improve reproducibility at larger scales, an applied vacuum was used for removing ethylene.¹⁹ Consequently, the yield and selectivity of the reaction remained reproducible at 43% (68% based on recovered starting material) and >95% *Z* with a shorter reaction time (6 h vs. 18 h). With enantiopure olefin **13** in hand, desilylation was performed using TBAF to provide the corresponding terminal alkyne in 92% yield (Scheme 3). Saponification of the ester afforded the carboxylic acid **16** in 99% yield. Esterification of acid **16** with secondary alcohol **3** was promoted by reaction with DCC and DMAP to provide the desired compound **2** in 62% yield.



Scheme 3. Synthesis of linear precursor **2** for macrocyclization to form the macrocyclic core of ivorenolide A.

With both key linear precursors in hand, attempted macrocyclization was performed first using the simplified model **2a** (Scheme 4). As such, the bis-alkyne **2a** was cyclized under slow addition conditions, using super-stoichiometric amounts of CuCl (12 equiv.) and ligand (TMEDA, 20 equiv.) in refluxing toluene. Slow addition was performed over 36 h and the refluxing reaction mixture (final concentration 0.2 mM) was left to stir for another 12 h to promote conversion of all the starting material **2a**. Macrocycle **1a** was isolated following silica gel chromatography in 36% yield. When identical reaction conditions were used to cyclize the more complex macrocyclization precursor **2**, the yield of the desired macrocycle **1** was higher at 55%. Next, the macrocyclization precursors were subjected to phase separation conditions at ~120 times the concentration employing reaction conditions previously developed for cyclization under microwave heating.²⁰ For the cyclization of **2a**, a 40% yield of macrocycle **1a** was isolated. Similar yields (30%) were also observed using the linear precursor **1**. Each bis-alkyne was observed to be sensitive to the basic conditions of the protocol for macrocyclization and it was hoped that the precise control over temperature/reaction time using continuous flow would be advantageous.²¹ For the model precursor **2a**, macrocyclizations under continuous flow conditions²² were evaluated with different ratios of PEG solvent to MeOH (Table 1). Based upon previous work,²³ residence times of 1-2 h were selected for study. Consequently, a low flow rate (0.167 mL/min) combined with a 20 mL reactor volume were necessary (two 10 mL reactor coils were connected in series). In addition, since higher ratios of PEG₄₀₀/MeOH typically provide higher selectivity for macrocyclization versus oligomerization, albeit with longer reaction times, the optimization of the macrocyclization was conducted with a 2 h residence time. When precursor **2a** was cyclized at 120 °C, with a residence time of 2 h in PEG₄₀₀/MeOH (1:1) a 30% yield of macrocycle **1a** was isolated. Efforts to boost yields through increasing the ratio of

PEG₄₀₀/MeOH to 4:1 resulted in lower yields, and a ratio of PEG₄₀₀/MeOH (8:1) required longer reaction times (4 h). Switching the solvent from PEG₄₀₀ to PPG₄₂₅, a poly(propylene)glycol solvent previously demonstrated to be efficient in “phase separation”-type macrocyclizations, provided the best yield of macrocycle **1a** (38-40% yield).

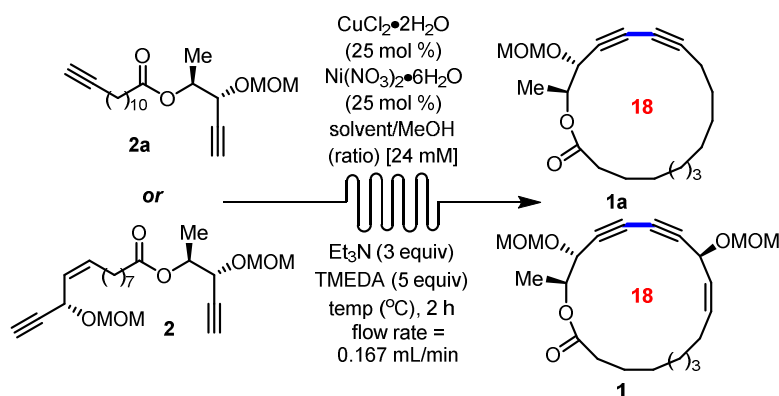


Scheme 4. Macrocyclizations under slow addition conditions (a) and macrocyclizations under phase separation/microwave heating (b) to form macrocycles **1** and **1a**. Ring sizes in red.

To demonstrate the feasibility of using the “phase separation” strategy alongside continuous flow for large scale preparation of macrolide type macrocycles, the macrocyclization (**2a**→**1a**) was repeated at gram scale and provided identical yields to what was observed at smaller scales (50-150 mg). Gram scale cyclization of diyne **2a** required 120 mL of the PPG₄₂₅:MeOH (2:1) solvent mixture, while the equivalent slow addition experiment would have required >14 L of PhMe. When a similar set of conditions were used for the macrocyclization of precursor **2**

possessing the additional *Z*-olefin and propargylic stereocenter, the best conditions surveyed utilized 120 °C, with a residence time of 2 h in PEG₄₀₀/MeOH (1:1) for a 52% yield of macrocycle **1**. The higher yield of macrocycle **1** (52%) versus the model macrocycle **1a** under similar reaction conditions could be explained by the effects of the additional *cis*-olefin and stereocenter in the respective precursor **2** versus **2a**. The addition of the olefin and hydroxyl motifs could promote a conformational bias to help bring the alkyne functionalities closer to one another.²⁴ Consequently, the use of the phase separation/continuous flow conditions for the preparation of the ivorenolide macrocycle **1** provided several advantages to using a traditional slow addition type strategy. In addition to providing a similar yield (55 vs 52% of **1**), reaction under the phase separation/continuous flow manifold were catalytic as opposed to using superstoichiometric quantities of ligand and metal source, the reaction time was significantly shortened (48 vs 2 h) and the concentration was greater by more than two orders of magnitude (0.2 vs 24 mM).

Table 1 Macrocyclizations using the phase separation strategy in continuous flow.



	PEG solvent	Ratio (PEG:MeOH)	Temp. (°C)	Yield (%) ^a
macrocyclization 2a → 1a				
1	PEG ₄₀₀	1:1	120	30 (<5)

2	PEG ₄₀₀	2:1	120	26 (<5)
3	PEG ₄₀₀	4:1	120	19 (24)
4	PEG ₄₀₀	8:1	120	14 (18) ^b
5	PPG ₄₂₅	2:1	120	38-40 ^c
macrocyclization 2 → 1				
6	PEG ₄₀₀	1:1	120	52 (0)
7	PEG ₄₀₀	2:1	120	37 (<5)
8	PEG ₄₀₀	4:1	100	27 (30)

^a Yields following chromatography. Recovered starting material in parentheses. ^b 4 h reaction time. ^c Reactions performed at 80 or 100 °C afforded similar yields with small amounts of unreacted **2a**. For ease of purification, the reaction was kept at 120 °C. Ring sizes in red.

CONCLUSIONS

In summary, a formal total synthesis of ivorenolide A has been accomplished using a macrocyclic catalytic oxidative coupling of terminal alkynes and a Z-selective cross metathesis as key steps. Macrocyclization has been demonstrated employing a phase separation/continuous flow method that is applicable to complex macrolides bearing chiral centers, steric hindrance about the alkynes and common protecting groups. The macrocyclization also described for the first time that continuous flow protocols allows for much more facile scale-up that would be highly problematic using high dilution strategies or microwave heating. The phase separation strategy produced good yields of the desired macrocycles employing catalysis in place of stoichiometric reagents, faster reaction times than the corresponding batch reactions and at concentrations ~120X greater than the slow addition strategy. Given the rarity of macrocyclizations performed under continuous flow, and the importance of macrocycles in both natural product synthesis and medicinal chemistry, the use of the phase separation/continuous flow method would be expected to have significant impact.

EXPERIMENTAL SECTION

All reactions that were carried out under anhydrous conditions were performed under an inert argon or nitrogen atmosphere in glassware that had previously been dried overnight at 120 °C or had been flame dried and cooled under a stream of argon or nitrogen.²⁵ All chemical products obtained were reagent quality. Tridec-12-ynoic acid²⁶, (±)-3-hydroxy-5-(triisopropylsilyl)pent-1-en-4-yne,¹⁸ (3*S*)-3-hydroxy-5-(triisopropylsilyl)pent-1-en-4-yne and Methyl dec-9-enoate²⁷ were prepared according to literature procedure. Anhydrous solvents (CH₂Cl₂, Et₂O, THF, DMF, toluene, and *n*-hexane) were dried and deoxygenated. Isolated yields reflect the mass obtained following flash column silica gel chromatography. Organic compounds were purified using the method reported by W. C. Still²⁸ and using silica gel (40-63 nm; 230-240 mesh). Analytical thin-layer chromatography (TLC) was performed on glass-backed silica gel 60 coated with a fluorescence indicator. Visualization of TLC plate was performed by UV (254 nm), KMnO₄ or *p*-anisaldehyde stains. All mixed solvent eluents are reported as v/v solutions. Concentration refers to removal of volatiles at low pressure on a rotary evaporator. All reported compounds were homogeneous by thin layer chromatography (TLC) and by ¹H NMR. NMR spectra were taken in deuterated CDCl₃ unless otherwise noted. Signals due to the solvent served as the internal standard (CHCl₃: δ 7.27 for ¹H, δ 77.0 for ¹³C). The acquisition parameters are shown on all spectra. The ¹H NMR chemical shifts and coupling constants were determined assuming first-order behavior. Multiplicity is indicated by one or more of the following: s (singlet), d (doublet), t (triplet), app t (apparent triplet), q (quartet), app quin(apparent quintet), m (multiplet), br (broad); the list of couplings constants (*J*) corresponds to the order of the multiplicity assignment.

Methyl (*S*)-2-((*tert*-butyldimethylsilyl)oxy)propanoate (5) TBSCl (8.68 g, 57.6 mmol, 1.2 equiv.) and imidazole (3.92 g, 57.6 mmol, 1.2 equiv.) were added to a solution of Methyl (*S*)-2-hydroxypropanoate (**4**) (4.6 mL, 48.0 mmol, 1.0 equiv.) in CH₂Cl₂ (120 mL) at 0 °C. The solution was stirred for 3 h at room temperature. Brine was then added and the organic and aqueous layers were separated. The aqueous phase was extracted with CH₂Cl₂ (3X) and the combined organic phases were washed with brine, dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure. Flash chromatography (6% EtOAc in hexanes) was performed to afford the product as a colorless oil (10.27 g, 98%). Spectral data were in accordance with those previously reported in the literature.²⁹

(*S*)-2-((*tert*-butyldimethylsilyl)oxy)propanal (6) DIBAL-H 1 M in hexanes (20.0 mL, 20.0 mmol, 1.5 equiv.) was added dropwise to a solution of methyl (*S*)-2-((*tert*-butyldimethylsilyl)oxy)propanoate (**5**) (2.92 g, 13.35 mmol, 1.0 equiv.) in anhydrous Et₂O (45 mL) at -78 °C and stirred for 3 h. The solution was then quenched with a solution of sodium and potassium tartrate and the organic and aqueous layers were separated. The aqueous layer was extracted with Et₂O (3X). The combined organic layers were washed with brine, dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure. Flash chromatography (10% Et₂O in hexanes) was performed to afford the product as a colorless oil (1.92 g, 77%). Spectral data were in accordance with those previously reported in the literature.⁶

(3*R*,4*S*)-4-((*tert*-butyldimethylsilyl)oxy)-1-(trimethylsilyl)pent-1-yn-3-ol (S1) *n*-BuLi 1.35 M in THF (11.5 mL, 15.6 mmol, 1.5 equiv.) was added dropwise to a solution of ethynyltrimethylsilane (2.2 mL, 15.6 mmol, 1.5 equiv.) in anhydrous THF (23 mL) at -78 °C. The solution was stirred for 2 h at 0 °C. (*S*)-2-((*tert*-butyldimethylsilyl)oxy)propanal (**6**) (1.96 g, 10.4 mmol, 1.0 equiv.) was added to the solution at -78 °C and stirred for an additional hour. The

solution was then quenched with a solution of sodium and potassium tartrate. The resulting mixture was vigorously stirred for 2 h before Et₂O (30 mL) was added to the mixture. The organic and aqueous layers were separated. The aqueous layer was extracted with Et₂O (3X). The combined organic layers were washed with brine, dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure. Flash chromatography (100% Hexanes to 4% EtOAc in hexanes) was performed to afford exclusively the desired diastereoisomer as a white solid (1.55 g, 52%). Spectral data were in accordance with those previously reported in the literature.³⁰

(5*R*,6*S*)-6,8,8,9,9-pentamethyl-5-((trimethylsilyl)ethynyl)-2,4,7-trioxa-8-siladecane (7) In a sealable tube, NaI (135 mg, 0.89 mmol, 10 mol%) was added to a solution of (3*R*,4*S*)-4-((*tert*-butyldimethylsilyl)oxy)-1-(trimethylsilyl)pent-1-yn-3-ol (**S1**) (2.58 g, 8.9 mmol, 1.0 equiv.) in CH₂Cl₂ (90 mL). The solution was cooled to 0 °C and *i*Pr₂NEt (3.13 mL, 17.9 mmol, 2.0 equiv.) and MOMCl (2.05 mL, 26.9 mmol, 3.0 equiv.) were added. The mixture was stirred for 18 h at 60 °C then quenched with water and the organic and aqueous layers were separated. The aqueous layer was extracted with CH₂Cl₂ (3X). The combined organic layers were washed with brine, dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure. Flash chromatography (100% Hexanes to 5 % EtOAc in hexanes) was performed to afford the product as a yellow oil (2.97 g, 99%). Spectral data were in accordance with those previously reported in the literature.⁷

(2*S*,3*R*)-3-(methoxymethoxy)pent-4-yn-2-ol (3) TBAF (1 M in THF) (53.9 mL, 53.9 mmol, 6 equiv.) was added to a solution of (5*R*,6*S*)-6,8,8,9,9-pentamethyl-5-((trimethylsilyl)ethynyl)-2,4,7-trioxa-8-siladecane (**7**) (2.97 g, 9.0 mmol, 1.0 equiv.) in anhydrous THF (45 mL) and stirred for 3 h at room temperature. The solution was then quenched with water and the organic and aqueous layers were separated. The aqueous layer was extracted with EtOAc (3X). The

combined organic layers were washed with brine, dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure. Flash chromatography (30 % EtOAc in hexanes) was performed to afford the product as a yellow oil (1.22 g, 94%). ¹H NMR (400 MHz, CDCl₃) δ 4.96 (d, *J* = 8 Hz, 1H), 4.70 (d, *J* = 8 Hz, 1H), 4.31-4.29 (m, 1H), 3.98-3.95 (m, 1H), 3.42 (s, 3H), 2.50 (d, *J* = 2 Hz, 1H), 2.38 (bs, 1H) 1.31 (d, *J* = 4 Hz, 3H) ppm. ¹³C{¹H} NMR (75 MHz, CDCl₃) δ 94.4, 79.0, 75.8, 70.8, 69.1, 55.9, 18.1 ppm. HRMS (ESI⁺) *m/z* calculated for C₇H₁₂NaO₃ [M+Na]⁺: 167.0679; found: 167.0675.

(2*S*,3*R*)-3-(methoxymethoxy)pent-4-yn-2-yl tridec-12-ynoate (2a) DCC (946 mg, 4.6 mmol, 2 equiv.), DMAP (840 mg, 6.9 mmol, 3 equiv.) and **(2*S*,3*R*)-3-(methoxymethoxy)pent-4-yn-2-ol (3)** (331 mg, 2.3 mmol, 1 equiv.) were added to a solution of tridec-12-ynoic acid **(8)** (723 mg, 3.4 mmol, 1.5 equiv.) in CH₂Cl₂ (10 mL) and stirred for 18 h at room temperature. The solution was then placed in the freezer for 12 h and the precipitated urea was filtered. Silica gel was added to the filtrate and the slurry was concentrated under reduced pressure. Flash chromatography (100% hexanes to 10% EtOAc in hexanes) was performed to afford the product as a colorless oil (579 mg, 75%). ¹H NMR (400 MHz, CDCl₃) δ 5.1-5.10 (m, 1H), 4.92 (d, *J* = 6.8 Hz, 1H), 4.64 (d, *J* = 6.9 Hz, 1H), 4.42 (dd, *J* = 4 Hz, *J* = 2.1 Hz, 1H), 3.40 (s, 3H), 2.45 (d, *J* = 2.2 Hz, 1H), 2.33 (t, *J* = 7.5 Hz, 2H), 2.19 (td, *J* = 7.1 Hz, *J* = 2.7 Hz, 2H), 1.95 (t, *J* = 2.7 Hz, 1H), 1.65-1.61 (m, 2H), 1.56-1.49 (m, 2H), 1.40-1.28 (m, 15H) ppm. ¹³C{¹H} NMR (75 MHz, CDCl₃) δ 173.1, 94.2, 84.8, 79.1, 75.0, 70.8, 68.0, 67.4, 55.7, 34.4, 29.40, 29.36, 29.2, 29.0 (2C), 28.7, 28.5, 24.9, 18.4, 15.1 ppm. HRMS (ESI⁺) *m/z* calculated for C₂₀H₃₆NO₄ [M+NH₄]⁺: 354.2639; found: 354.2648.

(3*S*)-3-(*N*-Boc-*L*-phenylalanine)-5-(triisopropylsilyl)pent-1-en-4-yne (S2) DCC (2.74 g, 13.3 mmol, 2 equiv.), DMAP (2.43 g, 19.9 mmol, 3 equiv.) and (±)-3-hydroxy-5-

(triisopropylsilyl)pent-1-en-4-yne (**rac-10**) (1.58 g, 6.64 mmol, 1 equiv.) were added to a solution of *N*-Boc-L-phenylalanine (2.64 g, 9.96 mmol, 1.5 equiv.) in CH₂Cl₂ (10 mL) and stirred for 18 h at room temperature. The solution was then placed in the freezer for 12 h and the precipitated urea was filtered. Silica gel was added to the filtrate and the slurry was concentrated under reduced pressure. Flash chromatography (100% hexanes to 7% Et₂O in hexanes) was performed to separate the diastereomers and isolate **S2** as a colorless oil (923 mg, 29%). ¹H NMR (400 MHz, CDCl₃) δ 7.29-7.15 (m, 5H), 5.92 (d, *J* = 4.4 Hz, 1H), 5.98-5.81 (m, 1H), 5.61 (d, *J* = 13.7 Hz, 1H), 5.34 (d, *J* = 9.8 Hz, 1H), 4.96 (d, *J* = 6.8 Hz, 1H), 4.63 (d, *J* = 5.8 Hz, 1H), 3.13-3.06 (m, 2H), 1.42 (s, 9H), 1.10-1.09 (m, 21 H) ppm. ¹³C{¹H} NMR (100 MHz, CDCl₃) δ 170.5, 155.0, 135.8, 132.5, 129.5, 129.4, 128.5, 127.0, 119.6, 119.4, 101.4, 89.7, 79.9, 65.6, 54.2, 37.9, 54.2, 37.9, 28.3, 18.5, 11.1 ppm. HRMS (ESI⁺) *m/z* calculated for C₂₈H₄₃NO₄SiNa [M+Na]⁺: 508.2854; found: 508.2865.

(±)-3-hydroxy-5-(triisopropylsilyl)pent-1-en-4-yne (10) The amino acid adduct (**S3**) (960 mg, 1.98 mmol, 1.0 equiv.) was dissolved in tetrahydrofuran (16 mL). Then LiOH (190 mg, 7.92 mmol, 4.0 equiv.) was added as an aqueous solution (4 mL). The reaction mixture was stirred at 65 °C for 18 h. The reaction was then cooled to room temperature and HCl (1 M) was added until the mixture was neutralized (pH = 7). Extraction with EtOAc (3 X 5 mL) was performed and the combined organic phases were washed with brine (15 mL). The organic phase was dried over Na₂SO₄ and concentrated under reduced pressure to afford the desired product as a white solid (421 mg, 89%). Spectral data were in accordance with those previously reported in the literature.¹⁸

(3*S*)-3-(methoxymethoxy)-5-(triisopropylsilyl)pent-1-en-4-yne (11) The alcohol (**10**) (1.50 g, 6.30 mmol, 1.00 equiv.) was dissolved in CH₂Cl₂ (31 mL). iPr₂NEt (2.19 mL, 12.6 mmol,

2.00 equiv.) was added to the solution. MOMCl (0.96 mL, 12.6 mmol, 2.00 equiv.) was carefully added at 0 °C and the reaction mixture was stirred at room temperature for 18 h. The reaction was quenched by addition of water (20 mL) and extracted with CH₂Cl₂ (2 x 15 mL). The combined organic phases were washed with brine, dried over Na₂SO₄ and concentrated under reduced pressure. Flash chromatography (5% Et₂O in hexanes) was performed to obtain the product as a colorless oil (1.42 g, 80%). ¹H NMR (CDCl₃, 400 MHz) δ = 5.94 (ddd, *J* = 17.0 Hz, 10.2 Hz, 5.5 Hz, 1H), 5.56 (dt, *J* = 17.0 Hz, 1.2 Hz, 1H), 5.28 (dt, *J* = 10.2 Hz, 1.2 Hz, 1H), 4.98 (d, *J* = 6.7 Hz, 1H), 4.90 (dt, *J* = 5.5 Hz, 1.2 Hz, 1H), 4.68 (d, *J* = 6.7 Hz, 1H), 3.41 (s, 3H), 1.10-1.03 (m, 21H) ppm; ¹³C{¹H} NMR (CDCl₃, 75 MHz) δ = 134.9, 117.7, 103.6, 93.7, 88.4, 66.7, 55.7, 18.6, 11.1 ppm; HRMS (ESI⁺) calculated for C₁₆H₃₀O₂SiNa [M + Na]⁺ 305.1907, found 305.1907.³¹

Methyl (11*S*, 9*Z*)-11-(methoxymethoxy)-13-(triisopropylsilyl)tridec-9-en-12-ynoate (13) A flame-dried sealable tube was charged with CH₂Cl₂ (2.75 mL), Methyl dec-9-enoate (254 mg, 1.38 mmol, 1.00 equiv.) and the ester (**12**) (390 mg, 1.38 mmol, 1.00 equiv.). The catalyst (**15b**) (47 mg, 0.069 mmol, 0.05 equiv.) was added and the tube was sealed. The reaction mixture was allowed to stir for 3 h at 60 °C. A second equivalent of Methyl dec-9-enoate (**12**) (254 mg, 1.38 mmol, 1.00 equiv.) was added and the reaction mixture was allowed to stir for an additional 3 h. During the reaction time, the mixture was put under vacuum for 5 seconds every hour to eliminate the ethylene formed. After being cooled down to room temperature, silica was added and the slurry was concentrated under reduced pressure. Flash chromatography (5 to 10% Et₂O in hexanes) was performed to afford the product as a colorless oil (258 mg, 43% (68% BRSM), >95:5 *Z* : *E*). ¹H NMR (CDCl₃, 400 MHz) δ = 5.64-5.52 (m, 2H), 5.14 (d, *J* = 8.2 Hz, 1H), 4.95 (d, *J* = 6.8 Hz, 1H), 4.63 (d, *J* = 6.8 Hz, 1H), 3.67 (s, 3H), 3.40 (s, 3H), 2.30 (t, *J* = 7.5 Hz, 2H),

2.17-2.11 (m, 2H), 1.66-1.60 (m, 2H), 1.42-1.29 (m, 8 H), 1.11-1.05 (m, 21 H) ppm; $^{13}\text{C}\{^1\text{H}\}$ NMR (CDCl_3 , 100 MHz) δ = 174.2, 133.9, 127.1, 105.2, 93.3, 86.6, 61.5, 55.6, 51.4, 34.1, 29.3, 29.11, 29.05, 29.03, 27.7, 24.9, 18.6, 11.1 ppm; HRMS (ESI^+) calculated for $\text{C}_{25}\text{H}_{46}\text{O}_4\text{SiNa}$ [$\text{M} + \text{Na}$] $^+$ 461.3058, found 461.3063.³²

Methyl (11*S*, 9*Z*)-11-(methoxymethoxy)tridec-9-en-12-ynoate (S3) The protected alkyne (**13**) (390 mg, 0.890 mmol, 1.00 equiv.) and THF (2.67 mL) was added to a flame-dried round-bottom flask under N_2 . TBAF (1 M in THF, 1.78 mL, 1.78 mmol, 2.0 equiv.) was slowly added and the reaction mixture was stirred at room temperature for 3 h. The reaction was quenched by addition of H_2O (2 mL) and extracted with Et_2O (2 x 5 mL). The combined organic phases were washed with H_2O (10 mL), dried over Na_2SO_4 and concentrated under reduced pressure. Flash chromatography (5% to 10% EtOAc in hexanes) was performed to afford the product as a colorless oil (230 mg, 92%). ^1H NMR (CDCl_3 , 400 MHz) δ = 5.69-5.62 (m, 1H), 5.54-5.48 (m, 1H), 5.13 (ddd, J = 8.8 Hz, 2.1 Hz, 0.9 Hz, 1H), 4.85 (d, J = 6.9 Hz, 1H), 4.63 (d, J = 6.9 Hz, 1H), 3.67 (s, 3H), 3.40 (s, 3H), 2.48 (d, J = 2.1 Hz, 1H), 2.30 (t, J = 7.5 Hz, 2H), 2.16-2.10 (m, 2H), 1.66-1.58 (m, 2H), 1.43-1.29 (m, 8H) ppm; $^{13}\text{C}\{^1\text{H}\}$ NMR (CDCl_3 , 100 MHz) δ = 174.2, 134.7, 126.4, 93.2, 81.8, 73.5, 60.5, 55.6, 51.4, 34.1, 29.2, 29.0 (2C), 28.9, 27.5, 24.9 ppm; HRMS (ESI^+) calculated for $\text{C}_{16}\text{H}_{26}\text{O}_4\text{Na}$ [$\text{M} + \text{Na}$] $^+$ 305.1723, found 305.1715.

(9*Z*, 11*S*)-11-(methoxymethoxy)tridec-9-en-12-ynoic acid (16) Methyl ester (**S3**) (251 mg, 0.890 mmol, 1.0 equiv.) was dissolved in tetrahydrofuran (4 mL). Then LiOH (85 mg, 3.56 mmol, 4.0 equiv.) was added as an aqueous solution (1 mL). The reaction mixture was stirred at 65 °C for 18 h. The reaction was then cooled to room temperature and HCl (1 M) was added until the mixture was neutralized ($\text{pH} = 7$). Extraction with EtOAc (3 X 5 mL) was performed and the combined organic phases were washed with brine (15 mL). The organic phase was dried over

Na₂SO₄ and concentrated under reduced pressure to afford the desired product as a low melting solid (238 mg, 99%). ¹H NMR (CDCl₃, 400 MHz) δ = 5.66 (dt, *J* = 10.6, 7.5 Hz, 1H), 5.52 (m, 1H), 5.13 (dd, *J* = 8.8, 2.2 Hz, 1H), 4.86 (d, *J* = 6.9 Hz, 1H), 4.64 (d, *J* = 6.9 Hz, 1H), 3.41 (s, 3H), 2.48 (d, *J* = 2.2 Hz, 1H), 2.36 (t, *J* = 7.5 Hz, 2H), 2.16-2.11 (m, 2H), 1.64-1.62 (m, 2H), 1.42-1.33 (m, 8H) ppm; ¹³C{¹H} NMR (CDCl₃, 100 MHz) δ = 179.8, 134.6, 126.3, 93.1, 81.6, 73.5, 60.5, 55.5, 33.9, 29.1, 28.9, 28.8 (2C), 27.4, 24.5 ppm; HRMS (ESI⁺) calculated for C₁₅H₂₃O₄ [M+H]⁺: 267.1602, found 267.1609.

(2*S*, 3*R*)-3-(methoxymethoxy)pent-4-yn-2-yl (2*S*, 3*Z*)-11-(methoxymethoxy)tridec-12-ynoate
(2) DCC (472 mg, 2.29 mmol, 2 equiv.), DMAP (419 mg, 3.44 mmol, 3 equiv.) and (2*S*, 3*R*)-3-(methoxymethoxy)pent-4-yn-2-ol (3) (165 mg, 1.15 mmol, 1 equiv.) were added to a solution of (9*Z*, 11*S*)-11-(methoxymethoxy)tridec-9-en-12-ynoic acid (307 mg, 1.15 mmol, 1 equiv.) in CH₂Cl₂ (4 mL) and stirred for 18 h at room temperature. The solution was then placed in the freezer for 12 h and the precipitated urea was filtered. Silica gel was added to the filtrate and the slurry was concentrated under reduced pressure. Flash chromatography (100% hexanes to 20% EtOAc in hexanes) was performed to afford the product as a colorless oil (282 mg, 62%). ¹H NMR (CDCl₃, 400 MHz) δ = 5.65 (dt, *J* = 11 Hz, 7.3 Hz, 1H), 5.51 (t, *J* = 8.9 Hz, 1H), 5.14-5.09 (m, 2H), 4.92 (d, *J* = 6.9 Hz, 1H), 4.85 (d, *J* = 6.9 Hz, 1H), 4.63 (d, *J* = 6.9 Hz, 2H), 4.42 (dd, *J* = 3.8 Hz, 2.1 Hz, 1H), 3.40 (s, 3H), 3.39 (s, 3H), 2.47 (dd, *J* = 9.9 Hz, 2.1 Hz, 2H), 2.33 (t, *J* = 7.5 Hz, 2H), 2.17-2.10 (m, 2H), 1.66-1.60 (m, 2H), 1.39-1.29 (m, 11H) ppm; ¹³C{¹H} NMR (CDCl₃, 100 MHz) δ = 173.0, 134.7, 126.4, 94.2, 93.3, 81.8, 79.1, 75.0, 73.5, 70.8, 67.4, 55.6, 34.4, 29.2, 29.1, 29.0, 27.5, 24.9, 15.1 ppm; HRMS (ESI⁺) *m/z* calculated for C₂₂H₃₄NaO₆ [M+Na]⁺: 417.2248; found: 417.2260.

(17*R*,18*S*)-17-(methoxymethoxy)-18-methyloxacyclooctadeca-13,15-diyne-2-one (1a): Slow

Addition Procedure: To a triple-neck round-bottom flask equipped with a stirring bar and a condenser, CuCl (154 mg, 1.56 mmol, 12 equiv.) and TMEDA (0.4 mL, 2.6 mmol, 20 equiv.) was added to PhMe (550 mL). The mixture was stirred and warmed at 110 °C. To the mixture, a solution of **2a** (44 mg, 0.13 mmol, 1 equiv.) in PhMe (50 mL) was slowly added over 36 h (0.023 mL/min) with a syringe pump. The mixture was stirred and heated for an additional 12 h. The reaction was then cooled down to room temperature and concentrated under reduced pressure. Flash chromatography was performed (5% to 20% EtOAc in hexanes) to afford the desired product as a colorless oil (15.6 mg, 36%). $[\alpha]_D^{25} = -0.221$ ($c = 0.0044$, MeOH); $^1\text{H NMR}$ (300 MHz, CDCl_3) δ 5.04 (app quint, $J = 6$ Hz, 1H), 4.93 (d, $J = 9$ Hz, 1H), 4.61 (d, $J = 6$ Hz, 1H), 4.30 (d, $J = 6$ Hz, 1H), 3.38 (s, 3H), 2.36-2.31 (m, 4H), 1.74-1.67 (m, 4H), 1.37-1.26 (m, 15H) ppm. $^{13}\text{C}\{^1\text{H}\}$ NMR (75 MHz, CDCl_3) δ 172.8, 94.2, 81.0, 71.4, 71.0, 70.7, 69.0, 65.1, 55.9, 35.3, 29.7, 29.2, 28.4, 27.5, 26.8, 26.3, 25.7, 24.9, 18.8, 17.4 ppm. **HRMS** (ESI^+) m/z calculated for $\text{C}_{20}\text{H}_{30}\text{NaO}_4$ $[\text{M}+\text{Na}]^+$: 357.2036; found: 357.2029. **Microwave Procedure:** To a microwave vial equipped with a stirring bar was dissolved the diyne **2a** (41 mg, 0.12 mmol, 1 equiv.) in MeOH. To the mixture was added polyethylene glycol 400 (3.75 mL), $\text{CuCl}_2 \cdot 2\text{H}_2\text{O}$ (5 mg, 0.03 mmol, 25 mol %) and $\text{Ni}(\text{NO}_3)_2 \cdot 6\text{H}_2\text{O}$ (8.7 mg, 0.03 mmol, 25 mol %) and the mixture was stirred at room temperature for 30 seconds or until the metals were solubilized. Oxygen was bubbled in the solution for 5 min then TMEDA (0.09 mL, 0.6 mmol, 5 equiv.) and Et_3N (0.05 mL, 0.36 mmol, 3 equiv.) were added and the mixture was stirred at room temperature for an additional 30 seconds. The vial was then sealed with a microwave cap. The reaction was warmed to 100 °C for 3 h. The crude mixture was loaded directly onto silica gel for purification by chromatography (10% to 20% EtOAc in hexanes) to afford the desired product as a colorless oil

(16 mg, 40%). **Continuous Flow Procedure:** To a 200 mL pear-shaped flask equipped with a stirring bar, $\text{CuCl}_2 \cdot 2\text{H}_2\text{O}$ (118 mg, 0.70 mmol, 25 mol%), $\text{Ni}(\text{NO}_3)_2 \cdot 6\text{H}_2\text{O}$ (204 mg, 0.70 mmol, 25 mol%), TMEDA (2.07 mL, 13.9 mmol, 5 equiv.) and Et_3N (1.16 mL, 8.34 mmol, 3 equiv.) was dissolved in MeOH (20 mL) and the mixture was stirred at room temperature for 30 seconds or until the metals were solubilized. Poly(propylene glycol) 425 (77.2 mL) was added and the mixture was stirred at room temperature for an additional 30 seconds. **2a** (935 mg, 2.78 mmol, 1 equiv.) was dissolved in 18.6 mL of MeOH then added to the solution. The reaction mixture was pumped into the flow reactor for a reaction time of 120 min (2 x 10 mL Stainless Steel reactors, with a temperature controlled 27 cm length section of tubing between reactors) at a flow rate of 0.167 mL/min at 120 °C. The flow reaction was conducted in a VapourTec R4 reactor and a R2+ pumping module. The continuous flow setup is ended with two in-line back pressures regulators (VapourTec 8 bar + IDEX 17 bar). Upon completion, the mixture was extracted with EtOAc, washed with water and the combined organic phases were washed with brine. The organic phase was dried over Na_2SO_4 and concentrated under reduced pressure. The crude mixture was purified by chromatography (5 to 10% EtOAc in hexanes) to afford the desire product as a yellowish oil (353 mg, 38%).

(10Z,12S,17R,18S)-12,17-di(methoxymethoxy)-18-methyloxacyclooctadec-10-ene-13,15-diyn-2-one (1): Slow Addition Procedure: To a triple-neck round-bottom flask equipped with a stirring bar and a condenser, CuCl (119 mg, 1.2 mmol, 12 equiv.) and TMEDA (0.3 mL, 2.0 mmol, 20 equiv.) was added to PhMe (405 mL). The mixture was stirred and warmed at 110 °C. To the mixture, a solution of **2** (40 mg, 0.10 mmol, 1 equiv.) in PhMe (50 mL) was slowly added over 24 h (0.035 mL/min) with a syringe pump. The mixture was stirred and heated for an additional 24 h. The reaction was then cooled down to room temperature and concentrated under

reduced pressure. Flash chromatography was performed (5% to 20% EtOAc in hexanes) to afford the desire product as a colorless oil (21.4 mg, 55%). $[\alpha]_D^{25} = -62.1$ ($c = 0.00145$, MeOH)

^1H NMR (400 MHz, CDCl_3) δ 5.63-5.56 (td, $J = 10.8, 5.5$ Hz, 1H), 5.49 (app t, $J = 10.9$ Hz, 1H), 5.20 (d, $J = 8$ Hz, 1H) 5.06-5.01 (m, 1H), 4.91 (d, $J = 6.9$ Hz, 1H), 4.81 (d, $J = 6.7$ Hz, 1H), 4.61 (t, $J = 5.5$ Hz, 1H), 4.28 (d, $J = 7.7$ Hz, 1H), 3.38 (s, 3H), 3.38 (s, 3H), 2.38-2.29 (m, 2H), 2.20-2.06 (m, 2H), 1.73-1.57 (m, 4H), 1.39-1.29 (m, 9H) ppm. **$^{13}\text{C}\{^1\text{H}\}$ NMR** (75 MHz, CDCl_3) δ 172.8, 134.3, 126.5, 94.4, 93.6, 75.7, 70.6, 70.5, 69.5, 68.9, 61.5, 56.0, 55.7, 35.2, 29.7, 29.5, 29.4, 28.6, 28.5, 27.7, 25.4, 17.6 ppm. Spectral data were in accordance with those previously reported in the literature.¹²

Microwave Procedure: To a microwave vial equipped with a stirring bar was dissolved the diyne (38 mg, 0.10 mmol, 1 equiv.) in MeOH (1.05 mL). To the mixture was added polyethylene glycol 400 (3.15 mL), $\text{CuCl}_2 \cdot 2\text{H}_2\text{O}$ (4.2 mg, 0.025 mmol, 25 mol %) and $\text{Ni}(\text{NO}_3)_2 \cdot 6\text{H}_2\text{O}$ (7 mg, 0.025 mmol, 25 mol %) and the mixture was stirred at room temperature for 30 seconds or until the metals were solubilized. Oxygen was bubbled in the solution for 5 min then TMEDA (0.07 mL, 0.5 mmol, 5 equiv.) and Et_3N (0.04 mL, 0.3 mmol, 3 equiv.) were added and the mixture was stirred at room temperature for an additional 30 seconds. The vial was then sealed with a microwave cap. The reaction was warmed to 100 °C for 3 h. The crude mixture was loaded directly onto silica gel for purification by chromatography (10 % EtOAc in hexanes) to afford the desire product as a colorless oil (11.5 mg, 30%).

Continuous Flow Procedure: To a 20mL-reaction vial equipped with a stirring bar, $\text{CuCl}_2 \cdot 2\text{H}_2\text{O}$ (3 mg, 0.018 mmol) and $\text{Ni}(\text{NO}_3)_2 \cdot 6\text{H}_2\text{O}$ (5.2 mg, 0.018 mmol) was dissolved in MeOH (1.5 mL) and the mixture was stirred at room temperature for 30 seconds or until the metals were solubilized. Polyethylene glycol 400 (1.5 mL), TMEDA (0.05 mL, 0.33 mmol) and Et_3N (0.03 mL, 0.22 mmol) were added and the mixture was stirred at room temperature for an additional 30 seconds.

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2
3 Diyne **2** (19.9 mg, 0.051 mmol, 1 equiv.) was mixed 2 mL of the previous solution. The mixture
4
5 was stirred at room temperature until everything was soluble then taken into a syringe. The
6
7 reaction mixture was injected using a 2 mL injection loop into the flow reactor for a reaction
8
9 time of 120 min (2 x 10 mL Stainless Steel reactors, with a temperature controlled 27 cm length
10
11 section of tubing between reactors) at a flow rate of 0.167 mL/min at 120 °C. The flow reaction
12
13 was conducted in a VapourTec R4 reactor and a R2+ pumping module. The continuous flow
14
15 setup is ended with two in-line back pressures regulators (VapourTec 8 bar + IDEX 17 bar).
16
17 Upon completion, silica gel was added to the collection flask and the volatiles were removed
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19 under vacuum. The crude mixture was purified by chromatography (20% EtOAc in hexanes) to
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21 afford the desire product as a colorless oil (10.2 mg, 52%).
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54 **SUPPORTING INFORMATION**

Characterization data for all new compounds and optimization data for the Z-selective metathesis. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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(31) The same procedure was used for the synthesis of *rac*-**11**. The product was obtained as a colorless oil (1.70 g, 80 %).

(32) A similar procedure was used for the synthesis of *rac*-**13**. The modifications were: the reaction was run for 18 h, there was no second equivalent of ester added, no vacuum was performed and 10 mol% catalyst was used. The product was obtained as a colorless oil (250 mg, 59 %).

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